〈Case Report〉

Development of primary central nervous system post-transplant lymphoproliferative disorder immediately after cytomegalovirus viremia in an MDS patient who received cord blood transplantation

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ABSTRACT Epstein–Barr virus (EBV) plays a central role in the pathogenesis of post-transplant lymphoproliferative disorder (PTLD), and EBV reactivation after allogenic hematopoietic stem cell transplantation (allo-HSCT) is highly correlated with cytomegalovirus (CMV) reactivation, which might be a risk factor for PTLD. We encountered a myelodysplastic syndrome patient with PTLD in the central nervous system who experienced sequential CMV and EBV reactivation immediately after allo-HSCT. Previous studies have suggested relationships between CMV and EBV reactivation and between CMV reactivation and PTLD. Our case suggests the importance of CMV monitoring in patients after allo-HSCT to prevent PTLD. doi：10.11482/KMJ-E201945097 *(Accepted on October 23, 2019)*

Key words：Cord blood transplantation, Cytomegalovirus, Epstein–Barr virus, Post-transplant lymphoproliferative disorder

INTRODUCTION

The development of post-transplant lymphoproliferative disorder (PTLD) following allogenic hematopoietic stem cell transplantation (allo-HSCT) is associated with immunosuppression caused by T cell depletion of the donor marrow, antithymocyte globulin (ATG) use, unrelated or HLA-mismatched grafts, acute and chronic graft versus host disease (GVHD), and advanced age at transplantation[1, 2)]. Epstein–Barr virus (EBV) has a central role in the pathogenesis of most PTLD cases[3)]. Immunosuppression results in reduced EBV-specific cytotoxic T-lymphocyte responses against EBV-infected B-cells, allowing the uncontrolled proliferation of EBV-infected lymphocytes. Cytomegalovirus (CMV) has major consequences after allo-HSCT, and CMV infection itself has been reported to reduce immune

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function[4]. A few studies have suggested that there is a relationship between CMV reactivation and EBV reactivation[4, 5]. Zallio F *et al.* claimed that the risk of EBV reactivation in allo-HSCT patients is highly related to CMV reactivation, which might be a risk factor for PTLD[5]. However, the precise relationships among CMV/EBV reactivation and PTLD are still unknown, and accordingly monitoring and treatment strategies are limited. Here, we report a rare case of primary central nervous system (PCNS)-PTLD, who exhibited sequential CMV and EBV reactivation immediately after cord blood transplantation (CBT).

CASE REPORT

The initial features of the patient have been reported previously[6]. In brief, a 60-year-old man underwent CBT in 2010 for myelodysplastic syndrome (refractory anemia with excess blasts-1, International Prognostic Scoring System (IPSS): Intermediate-2). The patient had a history of intestinal Behçet's disease and underwent sigmoidectomy 2 months prior to the CBT. No abnormal findings were noted at admission, during which neurological examinations were performed. The conditioning regimen consisted of 180 mg/m^2 fludarabine, 3.2 mg/m^2 busulfan, and 60 mg/m^2 melphalan, followed by 2.5 mg/kg ATG. The patient received 1.89 $\times$ 10^7 cord blood cells per kilogram of body weight. Baseline prophylaxis against GVHD involved tacrolimus and mycophenolate mofetil treatment. Tacrolimus was administered intravenously from day –1 at 0.03 mg/kg to day +27, where day 0 represents the day of CBT, and it was then administered orally after 27 days. A daily dose of 1,500 mg of mycophenolate mofetil was also administered orally from days 3 to 17. Successful engraftment was confirmed on day 15, with no sign of acute GVHD during hospitalization.

On day 45, a CMV antigenemia assay revealed

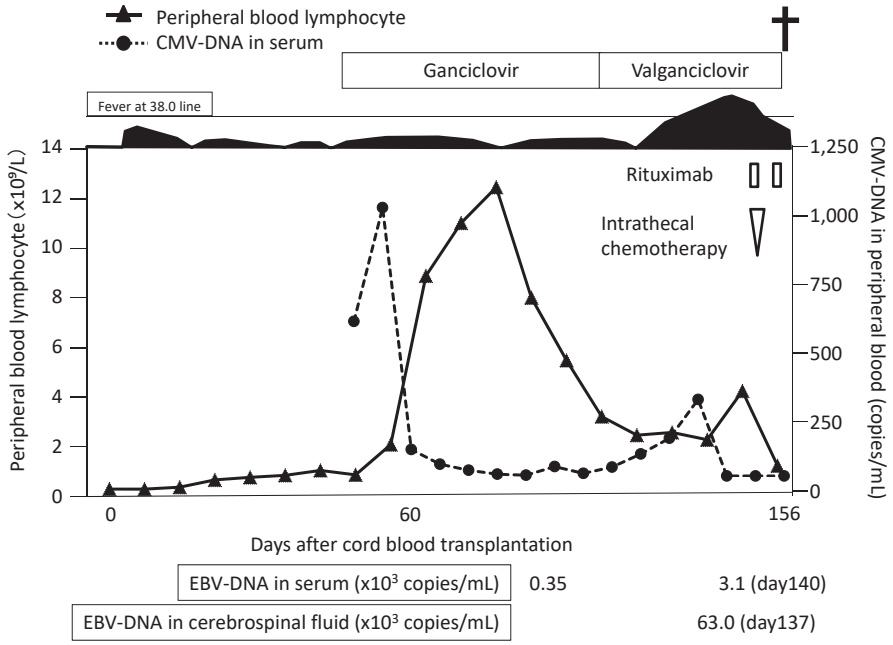

Fig. 1. Clinical course after cord blood transplantation. An elevation of CMV-DNA in serum was observed from day 45, and then the number of lymphocytes increased to respond. Cytomegalovirus was treated with ganciclovir and valganciclovir, but re-activated to 292 copies/mL on day 128. Subsequently, the serum EBV-DNA level rose to 3.1 $\times$ 10^3 copies/mL on day140, and EBV reactivation was observed. The patient developed PCNS-PTLD and was treated with rituximab and intrathecal chemotherapy but died on day 156.

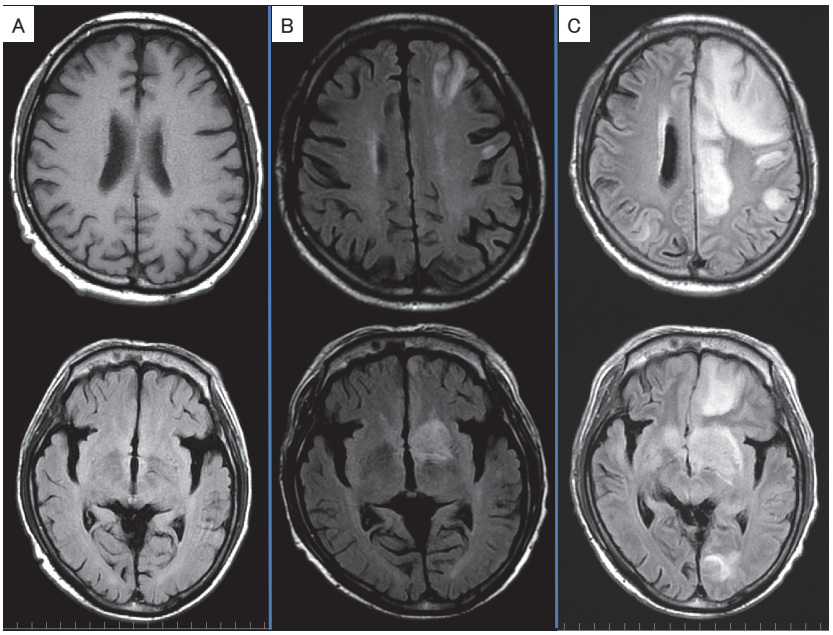

Fig. 2. Fluid-attenuated inversion recovery-magnetic resonance imaging (FLAIR-MRI) of the patient. From the left side, MRI before CBT (A), MRI at day 139 (B), and MRI at day 146 (C) are shown. MRI clearly indicates the rapid progression of the disease.

CMV viremia, which was initially treated with ganciclovir, followed by valganciclovir hydrochloride (Fig. 1). At the same time, an increase in peripheral blood lymphocytes was observed. These increased lymphocytes were morphologically reactive lymphocytes rather than tumor cells, then it was seemed to have increased in response to cytomegaloviremia. On day 56, the patient achieved a hematological recovery and complete remission. On day 133, he had a high fever, without any neurological symptoms. Subsequently, right concomitant deviation with disorientation was observed on day 135. Magnetic resonance imaging (MRI) of his brain revealed multiple hyperintensity regions on day 136 (Fig. 2). Cerebrospinal fluid lumbar puncture revealed increased class III atypical lymphocytes and his EBV-DNA level in the serum and cerebrospinal fluid was 3.1×10^3 and 63.0×10^3 copies/mL, respectively. Based on these results, the patient was diagnosed with PCNS-PTLD.

The patient was administered 375 mg/m^2 of rituximab therapy on day 138, and intrathecal chemotherapy with 40 mg of cytarabine and 10 mg of prednisolone was performed on day 144. However, no significant clinical therapeutic effect was obtained. The MRI performed on day 149 showed enlargement of the hyperintensity area, so the disease was apparently progressing (Fig. 2). The patient was additionally treated with rituximab therapy. However, the patient went into respiratory failure due to a cerebral herniation and died on day 156 after CBT.

An autopsy was performed with the approval of his family. The autopsy macroscopically revealed a markedly enlarged left cerebral hemisphere, with an increased brain weight to 1,550 g (Fig. 3A, 3B), hepatosplenomegaly, pleural effusion, ascites, sporadic pulmonary masses, and sporadic erosion of the digestive tract. In microscopic examination of tissues, abnormal lymphocyte proliferation was observed in the left cerebral hemisphere region (Fig. 3C, 3D). These lymphocytes were positive

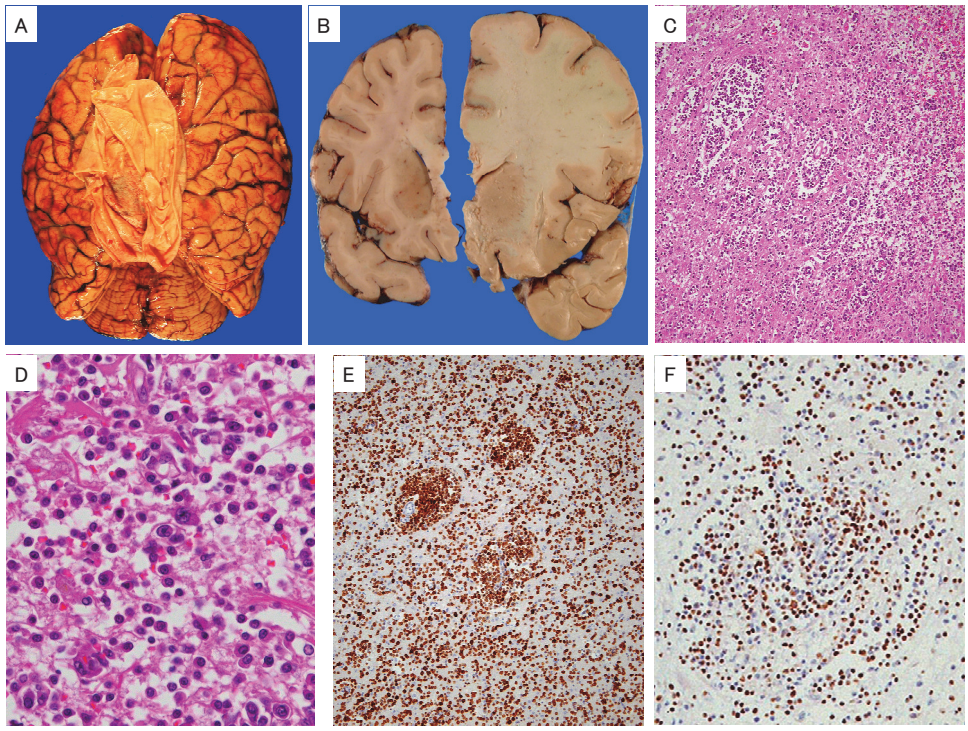

Fig. 3. Brain autopsy findings of the patient. A: Markedly enlarged left cerebral hemisphere. B: Markedly expansion of left cerebral hemisphere. C: Abnormal lymphocyte proliferation was observed in the left cerebral hemisphere region (magnification, x100). D: Medium-sized abnormal lymphocytes were diffusely proliferated (magnification, x400). These lymphocytes were positive for CD79a (E) and EBV-encoded small RNA (F) by immune-histological staining (magnification, x200).

for CD79a and EBV-encoded small RNA (EBER) (Fig. 3E, 3F), but negative for CD3 by immune-histological staining. From these results, the patient was diagnosed as EBV-associated monomorphic PTLD involving the brain, lung, digestive tract, and adrenal glands.

DISCUSSION

The incidence of PTLD in stem cell allograft recipients is reported to be 1–2%[7]. The risk of early-onset PTLD (<1 year) is highest with unrelated or HLA-mismatched related donors, selective T-cell depletion of donor bone marrow, and the use of ATG or anti-CD3 monoclonal antibodies[7]. PTLD isolated to the CNS following allo-HSCT is a rare presentation of an uncommon disease. Since the first report by Verschuur A *et al*., 13 cases of PCNS-PTLD related to HSCT have been recorded in the literature[2, 8], and these reports do not indicate a relationship between CMV reactivation and the development of PTLD. Seven out of 13 previous PCNS-PTLD patients died after disease progression or during treatment[2]. Similar to our patient, three of the seven patients had an aggressive clinical course and died within 1 month after the development of symptoms[2], emphasizing the difficulty of treating this disease. Because PCNS-PTLD following transplantation is rare, there is no consensus regarding the optimal treatment.

The etiology of PTLD is strictly related to EBV reactivation; therefore, a pre-emptive strategy may be effective. Zallio F *et al*. reported that among 101 consecutive patients who underwent allo-HSCT, 50 patients were CMV-positive after HSCT,

EBV reactivation was observed in 34 patients, and 16 patients were at a high risk for progression to PTLD, defined as serum EBV-DNA>10,000 copies/mL[5]. Variations in the time until the development of PCNS-PTLD, with a median of 4.4 years in solid organ transplantation patients[3] and 7 months following allo-HSCT[2], makes it difficult to apply this strategy to the prevention of PCNS-PTLD. Zallio F *et al*. suggested the importance of CMV monitoring, as an indicator of EBV reactivation, and the effective prevention of PTLD by pre-emptive rituximab therapy[5]. None of the patients in this previous study developed PTLD after a single infusion of 375 mg/m2 rituximab, indicating that the strategy seems to be effective, and unfortunately, our case reinforced the significance of their strategy.

The clinical course of our case suggests a relationship between CMV reactivation and subsequent EBV reactivation prior to the onset of PCNS-PTLD. Patients with higher human C-C chemokine receptor 5 (CCR5) expression are significantly more likely to exhibit EBV reactivation after allogeneic HSCT[9]. Additionally, CMV has been reported to upregulate the expression of CCR5 in central memory cord blood mononuclear cells[10], which might explain our observation that PTLD occurred soon after CMV reactivation in a patient who received CBT. From these results, monitoring of CMV reactivation can predict EB virus reactivation, and early treatment intervention may prevent the development of PTLD.

Rituximab is considered to have poor efficacy against CNS lesions due to its low penetration of the blood–brain barrier; therefore, it is unclear whether a pre-emptive strategy could prevent the development of PCNS-PTLD.

In conclusion, the EBV reactivation and PTLD occurred shortly after CMV viremia following CBT in our patient, suggesting a need for further studies on the relationship between sequential CMV and EBV reactivation after allo-HSCT and the occurrence of EBV-related PTLD, especially in patients who received CBT. Optimal strategies for the diagnosis and treatment of PCNS-PTLD after allo-HSCT remain to be determined.

CONFLICT OF INTEREST DISCLOSURES

The authors declare no potential conflicts of interest.

AUTHORS CONTRIBUTIONS

(1)The conception and design of the study, or acquisition of data, or analysis and interpretation of data: T.H., T.K., K.H., Y.M., H.N.

(2)Drafting the article or revising it critically for important intellectual content: T.T., H.W.

(3)Final approval of the version to be submitted: T.H., T.K., T.T.

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